Gabapentin for Alcohol Withdrawal: Gaba-gaba-doo, yet another use? We've got some work to do now.

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Conflict of Interest

- The author of this presentation has no conflicts of interest to disclose

Objectives

- Discuss the importance of classifying alcohol withdrawal severity
- Identify treatment gaps of current treatment options for alcohol withdrawal
- Evaluate existing literature on gabapentin use in alcohol withdrawal disorder

Alcohol Use Disorder

- 5-10% of world's population affected by alcohol use disorder
  - Problematic pattern of alcohol use
  - Tolerance
  - Withdrawal ←

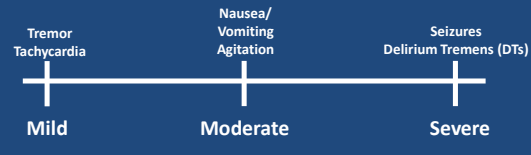
Sachdeva A, et al. J Clin Diagn Res. 2015; 9(9):VE01-VE07

Alcohol Withdrawal Syndrome (AWS)

- Cluster of symptoms occurring in individuals with alcohol dependence
  - Mild to severe
    - Tremor, tachycardia, nausea/vomiting, seizures, hallucinations, agitation, delirium tremens

Sachdeva A, et al. J Clin Diagn Res. 2015; 9(9):VE01-VE07

Severity



Sachdeva A, et al. J Clin Diagn Res. 2015; 9(9):VE01-VE07

Severity

Tremor
Tachycardia

Nausea/
Vomiting
Agitation

Seizures
Delirium Tremens (DTs)

Mild | Moderate | Severe

Sachdeva A, et al. J Clin Diagn Res. 2015; 9(9):VE01-VE07

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Diagnosis

- Amount and frequency of alcohol ingestion
- History of previous hospitalizations
  - Prior seizures?
  - Prior DTs?
- Relation between cessation of alcohol intake and onset of symptoms

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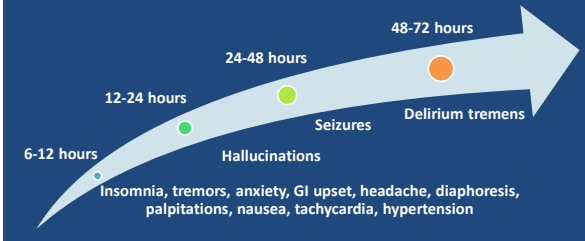
Symptom Timeline



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Diagnosis

- Amount and frequency of alcohol ingestion
- Relation between cessation of alcohol intake and onset of symptoms
- History of previous hospitalizations
- Severity assessment: Clinical Institute Withdrawal Assessment for Alcohol (CIWA)

Sachdeva A, et al. J Clin Diagn Res. 2015; 9(9):VE01-VE07

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CIWA Scale

Symptom Assessment	Severity Assessment	Treatment Plan
Anxiety Confusion Restlessness Mood Memory Nausea Heart Rate Sleep Quality Diaphoresis	None (0 points) Mild (1 point) Moderate (2 points) Severe (3 points)	≤ 8 points: Mild 9-15 points: Moderate ≥ 15 points: Severe

Bakhla AK, et al. J Addict. 2014; 2014: 745839

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Treatment

Goal:

1. Provide safe withdrawal
2. Use least amount of medicine possible to achieve rapid detoxification (CIWA)
3. Prepare patient for on-going treatment of alcohol dependence

Sachdeva A, et al. J Clin Diagn Res. 2015; 9(9):VE01-VE07
Muzyk AJ, et al. Am J Addict. 2013. 22:113

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Pathophysiology

- Nutritional deficiencies
- Interruption of constant CNS exposure to alcohol
  - Decrease in GABA levels and GABA-receptor sensitivity
    - Nervous system hyperactivity in absence of alcohol

Sachdeva A, et al. J Clin Diagn Res. 2015; 9(9):VE01-VE07

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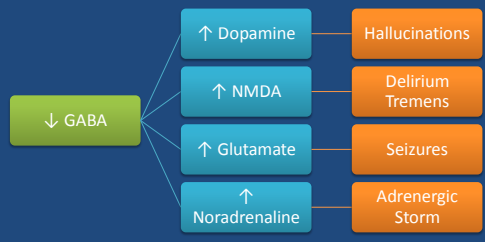
Pathophysiology



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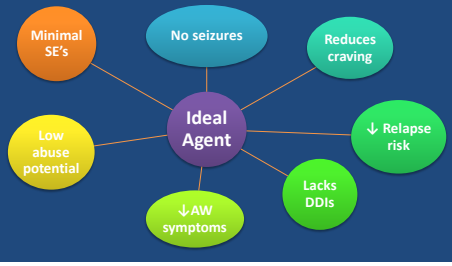
Pharmacotherapy Goals



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Pharmacotherapy

- Benzodiazepines (gold standard)
  - Diazepam, lorazepam, chlordiazepoxide
- Barbiturates
  - Phenobarbital
- Anticonvulsants
  - Carbamazepine (CBZ), valproic acid (VPA), gabapentin
- Adrenergic medicines
  - Clonidine, propranolol

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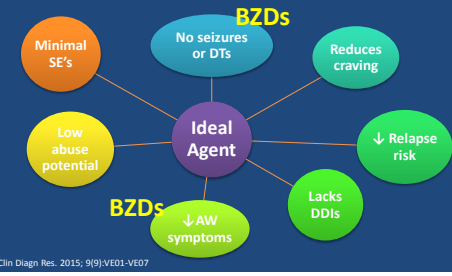
Pharmacotherapy Goals



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Clinical Dilemma with Benzodiazepines

- Increased craving
- Early relapse
- Increased alcohol consumption
- Memory deficits
- Respiratory depression
- Drug-drug interactions
- ABUSE

Maldonado, et al. Crit Care Clinic. 2008; 24: 657-722
Caputo, et al. Curr Pharm Des. 2010; 16(19): 2118-25.

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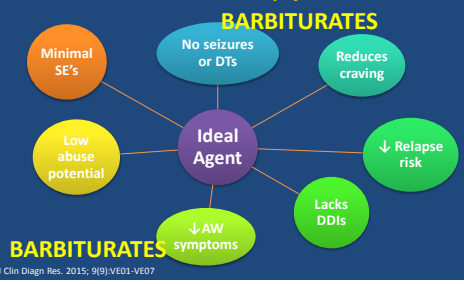
Pharmacotherapy Goals



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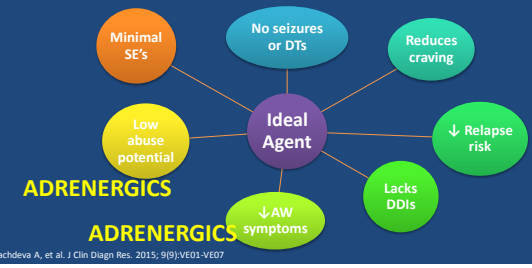
Pharmacotherapy Goals



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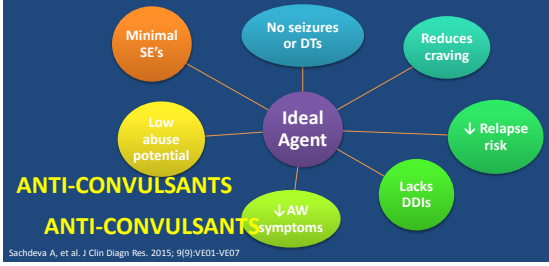
Pharmacotherapy Goals



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Gabapentin

- GABA analogue
- Anti-convulsive and anxiolytic properties
- Good tolerability and favorable safety profile
- Pure renal elimination
- Reduces craving and relapse risk
- Inexpensive

Watson WP, et al. Neuropharmacology. 1997; 36: 1369-75.

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Bonnet, et al. (1999)

- Four inpatients with moderate AWS and alcohol dependence for over five years
- Received gabapentin 400 mg QID
- Compared as-needed clomethiazole (CLO) requirements to previous admission
- Gabapentin led to reduced CLO requirements, no documented seizure occurrences

Bonnet U, et al. Pharmacopsychiatry. 1999; 32: 107-9.

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Bonnet, et al. (2003)

Objective	• To assess efficacy of gabapentin in the treatment of AWS
Design	• 2-center, double-blind, placebo-controlled
Population	• Moderate-Severe AWS according to MAWS Scale (57 total patients)
Interventions	• Gabapentin 400 mg QID vs. placebo • Patients received as needed clomethiazole (CLO)
Outcomes	• Primary: Amount of rescue CLO needed • Secondary: Course of MAWS scores within first 48 hours of AWS

MAWS = Mainz Alcohol Withdrawal Score

Bonnet U, et al. J Clin Psychopharmacol. 2003; 23: 514-19.

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Bonnet, et al. (2003)

Results	• No difference in number of CLO taken in initial 24 hours (P=0.96) • MAWS in first 48 hours not significantly different (P=0.39) • No seizures or delirium throughout treatment
Limitations	• Gabapentin dose may have been too low • Design quickly led to "rescue" • Clomethiazole may mask delayed effect of gabapentin
Conclusion	• Gabapentin 400 mg qid no better than placebo in reducing need for rescue clomethiazole for treatment of AWS

Bonnet U, et al. J Clin Psychopharmacol. 2003; 23: 514-19.

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Mariani et al. (2006)

Objective	• To assess efficacy of gabapentin in the management of AWS
Design	• Open-label, randomized, controlled trial
Population	• Inpatient detoxification patients with CIWA score > 10 and DSM—IV criteria for alcohol dependence (n=27)
Interventions	• Gabapentin taper (2400 mg first 24 hours, daily dose reduction 600 mg) • Phenobarbital taper (60 mg QID, daily dose reduction 60 mg)
Outcomes	• Primary: Proportion of treatment failures (need for ≥ 3 doses of breakthrough phenobarbital)

Mariani JJ, et al. Am J Addict. 2006; 15: 76-84.

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Mariani et al. (2006)

Results	• No difference in proportion of treatment failures • No difference in rescue medication requirement • No difference in AWS symptoms (craving, mood, anxiety)
Limitations	• Open-label (bias), small sample size • PRN phenobarbital could confound gabapentin effect • Dosing schedule of gabapentin potentially suboptimal
Conclusion	• Gabapentin may be equivalent to phenobarbital in the treatment of alcohol withdrawal

Mariani JJ, et al. Am J Addict. 2006; 15: 76-84.

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Myrick, et al. (2009)

Objective	• To evaluate alcohol use and symptom reduction of gabapentin compared to lorazepam in the treatment of AWS
Design	• Double-blind, randomized, dose-response trial
Population	• Outpatient detoxification patients with CIWA scores ≥ 10 (n=100)
Interventions	• Lorazepam 6 mg tapering to 4 mg over 4 days • Gabapentin (either 900 mg tapering to 600 mg or 1200 mg to 800 mg)
Outcomes	• Severity of alcohol withdrawal (CIWA scores) days 1-4 and days 5, 7, 12 • Alcohol use, measured via verbal report and alcohol breath levels

Myrick H, et al. Alcohol Clin Exp Res. 2009.;33(9): 1582-8.

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Myrick, et al. (2009)

Results	• CIWA score reduction superior in gabapentin group • Lorazepam group higher probability of relapse • Less craving, anxiety, and sedation in gabapentin group
Limitations	• Only moderate AWS severity • Participants in better general health • Small sample size
Conclusion	• Gabapentin was superior to lorazepam in the treatment of outpatients in moderate AWS (lower probability of drinking and clinically similar symptom reduction)

Myrick H, et al. Alcohol Clin Exp Res. 2009.;33(9): 1582-8.

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Bonnet, et al. (2010)

Objective	• To test a higher gabapentin entry dose in treating AWS
Design	• Open-label trial
Population	• Inpatients with CIWA scores ≥ 15 (n=37)
Interventions	• Entry dose 800 mg gabapentin given at baseline • Early-responders: 600 mg QID taper; Non-early responders: usual tx
Outcomes	• CIWA, HAMA, HAMD score trend over four-day treatment course • Adverse clinical effects throughout treatment course

Bonnet U, et al. Alcohol Alcohol. 2010;45(2):143-45

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Bonnet, et al. (2010)

Results
- CIWA < 15 in 27 (73%) patients after gabapentin load
- Two 'early-responders' developed seizures
- 'Non-responders' more severe AWS (P=0.026), longer treatment duration(P=0.05), higher HAMA/HAMD scores (P<0.001)

Limitations
- Open-label, small sample size, lack of comparator
- Lack of generalizability

Conclusion
- Non-response to gabapentin can be predicted by more severe AWS (mean CIWA score >20) with greater anxiety/depressive symptoms

Bonnet U, et al. Alcohol Alcohol. 2010;45(2):143-45

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What do YOU think?

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Clinical Trial Summary

	Bonnet 1999	Bonnet 2003	Mariani 2006	Myrick 2009	Bonnet 2010
Design	Case report	MC-DB-PC	OL-R-CT	DB-R-DR	OL
Population	Moderate AWS 4 inpatients	Moderate-Severe AWS	CIWA > 10 Inpatient	CIWA ≥ 10 Outpatient	CIWA ≥ 15 Inpatient
Intervention	Gaba 400 QID vs. Placebo	Gaba 400 QID vs. Placebo	Gaba vs. Phenobarb taper	Gaba 900 or 1200 vs. Lorazepam 6	Gaba load → 600 QID taper vs. CLO or CZP
Results	Reduced need for CLO administration	No. ↓ in CLO administration	No difference in CIWA ↓ or need for rescue	Gaba better improved CIWA and relapse	Gaba less effective when baseline CIWA > 20
Conclusion	Gaba reduces need for rescue medication	Gaba does not reduce need for rescue	Gaba equivalent to phenobarb in AWS treatment	Gaba superior to lorazepam in AWS treatment	Gaba load helpful only in reducing less severe AWS

MC=multicenter; DB=double-blind; PC=placebo-controlled; OL=open-label; R=randomized; DR=dose-related
Gaba=gabapentin; CLO=clomethiazole; Phenobarb=phenobarbital; CZP=clonazepam

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Limitations

LACK OF TRIAL CONSISTENCY!

How would YOU replicate this trial?

Dose?
- 400 mg QID?
- 600 mg TID?
- Loading strategy?

Population?
- Inpatient?
- Outpatient?

Outcomes?
- PRN requirements?
- MAWS reduction?
- CIWA reduction?
- Mood?

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Pharmacotherapy Goals

Reduces AW symptoms	BZD
Seizure prevention	X
Low side-effect incidence	
Few drug-drug interactions	
Low potential for abuse	
Decreases craving	
Decreases relapse	

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Pharmacotherapy Goals

Reduces AW symptoms	BZD	GABA
Seizure prevention	X	
Low side-effect incidence		X
Few drug-drug interactions		X
Low potential for abuse		X
Decreases craving		X
Decreases relapse		X

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Why not both?

Reduces AW symptoms	BZD + GABA
Seizure prevention	X
Low side-effect incidence	X
Few drug-drug interactions	X
Low potential for abuse	X
Decreases craving	X
Decreases relapse	X

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Future Direction

- Research Proposal
  - To investigate the use of adjunctive gabapentin with BZDs in the treatment of inpatient AWS
  - Primary Objective: determine whether adjunctive gabapentin leads to reduction in PRN BZD administration
  - Secondary Objective: evaluate whether adjunctive gabapentin leads to quicker, better treatment of AWS

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Conclusion

- Gabapentin effectively treats mild-moderate AWS
- Gabapentin effectively treats alcohol dependence
- Gabapentin is safe, and well-tolerated
- BZDs are current gold standard, but possess several limitations
- Mixed results regarding gabapentin ability to reduce need for rescue medication in AWS

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